PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 38147-0055	**FOR FURTHER ACTION**	See Form PCT/IPEA/416
International application No. PCT/US04/10059	International filing date *(day/month/year)* 01 April 2004 (01.04.2004)	Priority date *(day/month/year)* 01 April 2003 (01.04.2003)
International Patent Classification (IPC) or national classification and IPC IPC: **A61K 48/00**(2006.01);**C07H 21/04**(2006.01) USPC: 514/44;536/23.1		
Applicant INTRADIGM CORPORATION		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of ___ sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☐ *(sent to the applicant and to the International Bureau)* a total of ___ sheets, as follows:
      ☐ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) _____ , containing a sequence listing and/or tables related thereto, in electronic form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).
4. This report contains indications relating to the following items:
   - ☒ Box No. I Basis of the report
   - ☐ Box No. II Priority
   - ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - ☐ Box No. IV Lack of unity of invention
   - ☒ Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - ☐ Box No. VI Certain documents cited
   - ☐ Box No. VII Certain defects in the international application
   - ☒ Box No. VIII Certain observations on the international application

Date of submission of the demand	Date of completion of this report
01 November 2004 (01.11.2004)	01 June 2006 (01.06.2006)
Name and mailing address of the IPEA/ US Mail Stop PCT, Attn: IPEA/US Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450 Facsimile No. (571) 273-3201	Authorized officer Tracy Vivlemore Telephone No. 571-272-1600

Form PCT/IPEA/409 (cover sheet)(April 2005)

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Box No. I Basis of the report

1. With regard to the **language**, this report is based on:

☐ the international application in the language in which it was filed.

☐ a translation of the international application into _____, which is the language of a translation furnished for the purposes of:

☐ international search (under Rules 12.3 and 23.1(b))

☐ publication of the international application (under Rule 12.4(a))

☐ international preliminary examination (under Rules 55.2(a) and/or 55.3(a))

2. With regard to the **elements** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

☒ the international application as originally filed/furnished

☒ the description:
pages 1-88 as originally filed/furnished
pages* NONE received by this Authority on _____
pages* NONE received by this Authority on _____

☒ the claims:
pages 89-95 as originally filed/furnished
pages* NONE as amended (together with any statement) under Article 19
pages* NONE received by this Authority on _____
pages* NONE received by this Authority on _____

☒ the drawings:
pages 1-66 as originally filed/furnished
pages* NONE received by this Authority on _____
pages* NONE received by this Authority on _____

☒ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing.

3. ☐ The amendments have resulted in the cancellation of:

☐ the description, pages _____
☐ the claims, Nos. _____
☐ the drawings, sheets/figs _____
☐ the sequence listing (*specify*): _____
☐ any table(s) related to the sequence listing (*specify*): _____

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

☐ the description, pages _____
☐ the claims, Nos. _____
☐ the drawings, sheets/figs _____
☐ the sequence listing (*specify*): _____
☐ any table(s) related to the sequence listing (*specify*): _____

* *If item 4 applies, some or all of those sheets may be marked "superseded."*

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Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims 1-43 and 54-73	YES
	Claims NONE	NO
Inventive Step (IS)	Claims 1-32	YES
	Claims 33-43 and 54-73	NO
Industrial Applicability (IA)	Claims 1-43 and 54-73	YES
	Claims none	NO

2. Citations and Explanations (Rule 70.7)

Claims 1-32 meet the criteria set out in PCT Article 33(2)-(3), because the prior art does not teach or fairly suggest treatment of disease with a composition that serves to enhance expression of ICT1030. It is noted that antibodies directed to BA46 (another name for ICT1030) are known, however there is no teaching in the art that these antibodies serve to enhance expression or activity of ICT1030.

Claims 33-37, 43, 54-59 and 65 lack an inventive step under PCT Article 33(3) as being obvious over Gorza et al. in view of Taylor et al., Baracchini et al. and Cai et al.
Gorza et al. teach antisense compounds and methods that target grp94 and inhibit its expression.
Taylor et al. teach that antisense oligonucleotides can be synthesized to inhibit the expression of any protein provided the cDNA sequence is known. Taylor et al. also indicate that making and using such oligos are available to those of ordinary skill in the art and teach that one needs to screen only 3-6 oligos to find one that inhibits its target 66-95% (p. 565).
Baracchini et al. teach that antisense oligonucleotides can be used for research purposes. Table 1 exemplifies the successful practice of antisense design taught at columns 8-10. Baracchini is considered to comprise a detailed blueprint for how to make and use inhibitory antisense oligos to target any known gene.
Cai et al. teach that in murine tumors expression of grp94 correlates strongly with tumor size, with small tumors expressing small amounts of grp94 and large tumors expressing larger amounts of grp94.
The invention lacks an inventive step because it would have been obvious to generate antisense sequences to grp 94 as taught by Gorza et al. for inhibition of grp94 expression to treat a disease such as cancer. Based on the teachings of Gorza et al. that antisense oligonucleotides decrease grp94 expression, the teachings of Taylor et al. and Baracchini et al. that antisense oligonucleotides can be targeted to any protein for which the cDNA is known and the teaching of Cai et al. that grp94 expression correlates with tumor size, one would be motivated to use oligonucleotides to decrease expression of grp 94 in order to decrease tumor size.

Claims 33-43 and 54-73 lack an inventive step under PCT Article 33(3) as being obvious over the prior art as applied in the immediately preceding paragraph and further in view of Fire et al. Fire et al teach the use of double stranded RNAs to inhibit gene expression. Fire teaches that such RNAs can be produced by expression vector and also teaches that this method of inhibiting gene expression has advantages over antisense oligonucleotides. Based on the teachings of Fire et al. that dsRNAs inhibit gene expression and have advantages over antisense oligonucleotides, the invention set forth in claims 38-42, 60-64 and 66-73 of inhibition of grp94 gene expression using double stranded RNAs cannot be said to have an inventive step.

Claims 1-43 and 54-73 meet the criteria set out in PCT Article 33(4), and thus have industrial applicability because the subject matter claimed can be made or used in industry.

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Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

Claims 1-26 and 28-32 are objected to as lacking clarity under PCT Rule 66.2(a)(v) because the claims are not fully supported by the description. The application, as originally filed, did not describe: compositions that comprised of nucleic acids or antibodies that treat a disease, particularly cancer, by enhancing expression or activity of ICT1030. The specification describes nucleic acid inhibitors of ICT1030 but does not provide the structures of nucleic acids or antibodies that have the function of enhancing the expression or activity of ICT1030.

Claims 1-26 and 29-32 are objected to as lacking clarity under PCT Rule 66.2(a)(v) because of the claims are not fully supported by the description. The description does not disclose the claimed invention in a manner sufficiently clear and complete for the claimed invention to be carried out by a person skilled in the art because: the claims are directed to methods that involve administering nucleic acids to a whole animal for the purpose of altering expression of a gene. The specification describes general guidance of formulation, dosage and route of administration. The examples described in the specification involve administration to cultured cells. The route of administration used to deliver nucleic acids to cultured cells is not considered predictive of ability to deliver to a cell in an animal. Use of nucleic acids for therapeutic purposes is considered to be unpredictable because of problems with delivery to a specific tissue and duration of effect. One of skill in the art would not know how to deliver a nucleic acid to an animal and ensure the nucleic acid reached a particular cell or type of cell in an amount in an amount sufficient to have a measurable effect. The current level of skill in the art is such that delivery, dosage and formulation for every nucleic acid must be determined empirically; the general guidance provided by the specification does not allow the skilled artisan to perform the claimed methods without trial and error experimentation.

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Supplemental Box Relating to Sequence Listing

Continuation of Box No. I, item 2:

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application and necessary to the claimed invention, this report was established on the basis of:

a. type of material

☒ a sequence listing

☐ table(s) related to the sequence listing

b. format of material

☒ on paper

☒ in electronic form

c. time of filing/furnishing

☐ contained in the international application as filed

☐ filed together with the international application in electronic form

☒ furnished subsequently to this Authority for the purposes of search and/or examination

☐ received by this Authority as an amendment* on _____

2. ☒ In addition, in the case that more than one version or copy of a sequence listing and/or table(s) relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

3. Additional comments:

* *If item 4 in Box No. I applies, the listing and/or table(s) related thereto, which form part of the basis of the report, may be marked "superseded."*